



SEQUENCE LISTING

<110> Samuel Davis, Nicholas W. Gale, George D. Yancopoulos, and Neil Stahl

<120> METHOD OF ENHANCING THE BIOLOGICAL ACTIVITY OF LIGANDS

<130> REG 670-A-US

<140> USSN 09/868,677

<141> 2001-10-01

<150> PCT/US99/30900

<151> 1999-12-23

<150> 60/113,387

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Asp Cys Ala Asp Val Tyr Gln Ala Gly Phe Asn Lys Ser Gly Ile Tyr
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act att tat att aat aat atg cca gaa ccc aaa aag gtg ttt tgc aat 144
Thr Ile Tyr Ile Asn Asn Met Pro Glu Pro Lys Lys Val Phe Cys Asn
35 40 45

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Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
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Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
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35 40 45
Met Asp Val Asn Gly Gly Gly Trp Thr Val Ile Gln His Arg Glu Asp
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Gly Ser Leu Asp Phe Gln Arg Gly Trp Lys Glu Tyr Lys Met Gly Phe
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Gly Asn Pro Ser Gly Glu Tyr Trp Leu Gly Asn Glu Phe Ile Phe Ala
85 90 95
Ile Thr Ser Gln Arg Gln Tyr Met Leu Arg Ile Glu Leu Met Asp Trp
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Glu Gly Asn Arg Ala Tyr Ser Gln Tyr Asp Arg Phe His Ile Gly Asn
115 120 125
Glu Lys Gln Asn Tyr Arg Leu Tyr Leu Lys Gly His Thr Gly Thr Ala
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Gly Lys Gln Ser Ser Leu Ile Leu His Gly Ala Asp Phe Ser Thr Lys
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Asp Ala Asp Asn Asp Asn Cys Met Cys Lys Cys Ala Leu Met Leu Thr
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Gly Gly Trp Trp Phe Asp Ala Cys Gly Pro Ser Asn Leu Asn Gly Met
180 185 190
Phe Tyr Thr Ala Gly Gln Asn His Gly Lys Leu Asn Gly Ile Lys Trp
195 200 205
His Tyr Phe Lys Gly Pro Ser Tyr Ser Leu Arg Ser Thr Thr Met Met
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Ile Arg Pro Leu Asp Phe Gly Pro Ala Pro Phe Arg Asp Cys Ala Asp
225 230 235 240
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0986677 100101

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Arg	Gln	Tyr	Met	Leu	Arg	Ile	Glu	Leu	Met	Asp	Trp	Glu	Gly	Asn	Arg
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Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys
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Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln
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35 40 45	
atg gaa gct gga gga ggc ggg tgg aca att att cag cga cgt gag gat	192
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ggc agc gtt gat ttt cag agg act tgg aaa gaa tat aaa gtg gga ttt	240
Gly Ser Val Asp Phe Gln Arg Thr Trp Lys Glu Tyr Lys Val Gly Phe	
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ggt aac cct tca gga gaa tat tgg ctg gga aat gag ttt gtt tcg caa	288
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ctg act aat cag caa cgc tat gtg ctt aaa ata cac ctt aaa gac tgg	336
Leu Thr Asn Gln Gln Arg Tyr Val Leu Lys Ile His Leu Lys Asp Trp	
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180 185 190	
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Tyr Tyr Pro Gln Arg Gln Asn Thr Asn Lys Phe Asn Gly Ile Lys Trp	
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tac tac tgg aaa ggc tca ggc tat tcg ctc aag gcc aca acc atg atg	672
Tyr Tyr Trp Lys Gly Ser Gly Tyr Ser Leu Lys Ala Thr Thr Met Met	
210 215 220	

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ctc acc gtc ctg cac cag gac tgg ctg aat ggc aag gag tac aag tgc	1680
Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys	
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Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser	
565 570 575	
aaa gcc aaa ggg cag ccc cga gaa cca cag gtg tac acc ctg ccc cca	1776
Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro	
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tcc cgg gat gag ctg acc aag aac cag gtc agc ctg acc tgc ctg gtc	1824
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Gly	Asn	Pro	Ser	Gly	Glu	Tyr	Trp	Leu	Gly	Asn	Glu	Phe	Val	Ser	Gln
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Leu	Thr	Asn	Gln	Gln	Arg	Tyr	Val	Leu	Lys	Ile	His	Leu	Lys	Asp	Trp
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Glu	Gly	Asn	Glu	Ala	Tyr	Ser	Leu	Tyr	Glu	His	Phe	Tyr	Leu	Ser	Ser
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Gly	Lys	Ile	Ser	Ser	Ile	Ser	Gln	Pro	Gly	Asn	Asp	Phe	Ser	Thr	Lys
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Gly	Gly	Trp	Trp	Phe	Asp	Ala	Cys	Gly	Pro	Ser	Asn	Leu	Asn	Gly	Met
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Tyr	Tyr	Pro	Gln	Arg	Gln	Asn	Thr	Asn	Lys	Phe	Asn	Gly	Ile	Lys	Trp
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Trp	Phe	Asp	Ala	Cys	Gly	Pro	Ser	Asn	Leu	Asn	Gly	Met	Tyr	Tyr	Pro
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Gln	Arg	Gln	Asn	Thr	Asn	Lys	Phe	Asn	Gly	Ile	Lys	Trp	Tyr	Tyr	Trp
			420					425					430		
Lys	Gly	Ser	Gly	Tyr	Ser	Leu	Lys	Ala	Thr	Thr	Met	Met	Ile	Arg	Pro
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Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val
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Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser
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Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp
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Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His
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Asp	Cys	Ala	Asp	Val	Tyr	Gln	Ala	Gly	Phe	Asn	Lys	Ser	Gly	Ile	Tyr	
			20					25					30			
act	att	tat	att	aat	aat	atg	cca	gaa	ccc	aaa	aag	gtg	ttt	tgc	aat	144
Thr	Ile	Tyr	Ile	Asn	Asn	Met	Pro	Glu	Pro	Lys	Lys	Val	Phe	Cys	Asn	
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atg	gat	gtc	aat	ggg	gga	ggg	tgg	act	gta	ata	caa	cat	cgt	gaa	gat	192
Met	Asp	Val	Asn	Gly	Gly	Gly	Trp	Thr	Val	Ile	Gln	His	Arg	Glu	Asp	
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gga	agt	cta	gat	ttc	caa	aga	ggc	tgg	aag	gaa	tat	aaa	atg	ggg	ttt	240
Gly	Ser	Leu	Asp	Phe	Gln	Arg	Gly	Trp	Lys	Glu	Tyr	Lys	Met	Gly	Phe	
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gga	aat	ccc	tcc	ggg	gaa	tat	tgg	ctg	ggg	aat	gag	ttt	att	ttt	gcc	288

Gly	Asn	Pro	Ser	Gly	Glu	Tyr	Trp	Leu	Gly	Asn	Glu	Phe	Ile	Phe	Ala		
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att	acc	agt	cag	agg	cag	tac	atg	cta	aga	att	gag	tta	atg	gac	tgg		336
Ile	Thr	Ser	Gln	Arg	Gln	Tyr	Met	Leu	Arg	Ile	Glu	Leu	Met	Asp	Trp		
			100					105					110				
gaa	ggg	aac	cga	gcc	tat	tca	cag	tat	gac	aga	ttc	cac	ata	gga	aat		384
Glu	Gly	Asn	Arg	Ala	Tyr	Ser	Gln	Tyr	Asp	Arg	Phe	His	Ile	Gly	Asn		
		115					120					125					
gaa	aag	caa	aac	tat	agg	ttg	tat	tta	aaa	ggg	cac	act	ggg	aca	gca		432
Glu	Lys	Gln	Asn	Tyr	Arg	Leu	Tyr	Leu	Lys	Gly	His	Thr	Gly	Thr	Ala		
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gga	aaa	cag	agc	agc	ctg	atc	tta	cac	ggg	gct	gat	ttc	agc	act	aaa		480
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Asp	Ala	Asp	Asn	Asp	Asn	Cys	Met	Cys	Lys	Cys	Ala	Leu	Met	Leu	Thr		
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gga	gga	tgg	tgg	ttt	gat	gct	tgt	ggc	ccc	tcc	aat	cta	aat	gga	atg		576
Gly	Gly	Trp	Trp	Phe	Asp	Ala	Cys	Gly	Pro	Ser	Asn	Leu	Asn	Gly	Met		
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Phe	Tyr	Thr	Ala	Gly	Gln	Asn	His	Gly	Lys	Leu	Asn	Gly	Ile	Lys	Trp		
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Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro		
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Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser		
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Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp		
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cct	gag	gtc	aag	ttc	aac	tgg	tac	gtg	gac	ggc	gtg	gag	gtg	cat	aat		912
Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn		
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Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val		
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gtc	agc	gtc	ctc	acc	gtc	ctg	cac	cag	gac	tgg	ctg	aat	ggc	aag	gag		1008
Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu		

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Tyr Ser Gln Tyr Asp Arg Phe His Ile Gly Asn Glu Lys Gln Asn Tyr	
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Arg Leu Tyr Leu Lys Gly His Thr Gly Thr Ala Gly Lys Gln Ser Ser	
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ctg atc tta cac ggt gct gat ttc agc act aaa gat gct gat aat gac	1872
Leu Ile Leu His Gly Ala Asp Phe Ser Thr Lys Asp Ala Asp Asn Asp	
610 615 620	
aac tgt atg tgc aaa tgt gcc ctc atg tta aca gga gga tgg tgg ttt	1920
Asn Cys Met Cys Lys Cys Ala Leu Met Leu Thr Gly Gly Trp Trp Phe	
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gat gct tgt ggc ccc tcc aat cta aat gga atg ttc tat act gcg gga	1968
Asp Ala Cys Gly Pro Ser Asn Leu Asn Gly Met Phe Tyr Thr Ala Gly	
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Gln Asn His Gly Lys Leu Asn Gly Ile Lys Trp His Tyr Phe Lys Gly	
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cca agt tac tcc tta cgt tcc aca act atg atg att cga cct tta gat	2064
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Gly Ser Leu Asp Phe Gln Arg Gly Trp Lys Glu Tyr Lys Met Gly Phe	
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Gly Asn Pro Ser Gly Glu Tyr Trp Leu Gly Asn Glu Phe Ile Phe Ala	
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Glu Gly Asn Arg Ala Tyr Ser Gln Tyr Asp Arg Phe His Ile Gly Asn	
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Glu Lys Gln Asn Tyr Arg Leu Tyr Leu Lys Gly His Thr Gly Thr Ala	
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Gly Lys Gln Ser Ser Leu Ile Leu His Gly Ala Asp Phe Ser Thr Lys	
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Gly Gly Trp Trp Phe Asp Ala Cys Gly Pro Ser Asn Leu Asn Gly Met	
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Ile	Arg	Pro	Leu	Asp	Phe	Gly	Pro	Gly	Glu	Pro	Lys	Ser	Cys	Asp	Lys
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Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro
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Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
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Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
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Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys
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Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
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Lys	Gly	Gly	Gly	Gly	Ser	Gly	Ala	Pro	Phe	Arg	Asp	Cys	Ala	Asp	Val
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Gln	Arg	Gly	Trp	Lys	Glu	Tyr	Lys	Met	Gly	Phe	Gly	Asn	Pro	Ser	Gly
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Gln	Tyr	Met	Leu	Arg	Ile	Glu	Leu	Met	Asp	Trp	Glu	Gly	Asn	Arg	Ala
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Tyr	Ser	Gln	Tyr	Asp	Arg	Phe	His	Ile	Gly	Asn	Glu	Lys	Gln	Asn	Tyr
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	610					615					620				
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Gln	Asn	His	Gly	Lys	Leu	Asn	Gly	Ile	Lys	Trp	His	Tyr	Phe	Lys	Gly
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680

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Asp Cys Ala Glu Val Phe Lys Ser Gly His Thr Thr Asn Gly Ile Tyr	
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Thr Leu Thr Phe Pro Asn Ser Thr Glu Glu Ile Lys Ala Tyr Cys Asp	
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Gly Ser Val Asp Phe Gln Arg Thr Trp Lys Glu Tyr Lys Val Gly Phe	
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Gly Asn Pro Ser Gly Glu Tyr Trp Leu Gly Asn Glu Phe Val Ser Gln	
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ctg act aat cag caa cgc tat gtg ctt aaa ata cac ctt aaa gac tgg	336
Leu Thr Asn Gln Gln Arg Tyr Val Leu Lys Ile His Leu Lys Asp Trp	
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Glu Gly Asn Glu Ala Tyr Ser Leu Tyr Glu His Phe Tyr Leu Ser Ser	
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Glu Glu Leu Asn Tyr Arg Ile His Leu Lys Gly Leu Thr Gly Thr Ala	
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Asp Gly Asp Asn Asp Lys Cys Ile Cys Lys Cys Ser Gln Met Leu Thr	
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Tyr Tyr Trp Lys Gly Ser Gly Tyr Ser Leu Lys Ala Thr Thr Met Met	
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Ile Arg Pro Ala Asp Phe Gly Gly Pro Gly Glu Pro Lys Ser Cys Asp	
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Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly	
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Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile	
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Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu	
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Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr	
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Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp	
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Glu	Tyr	Trp	Leu	Gly	Asn	Glu	Phe	Val	Ser	Gln	Leu	Thr	Asn	Gln	Gln		
	545				550				555						560		
1728																	
cgc	tat	gtg	ctt	aaa	ata	cac	ctt	aaa	gac	tgg	gaa	ggg	aat	gag	gct		
Arg	Tyr	Val	Leu	Lys	Ile	His	Leu	Lys	Asp	Trp	Glu	Gly	Asn	Glu	Ala		
			565						570					575			
1776																	
tac	tca	ttg	tat	gaa	cat	ttc	tat	ctc	tca	agt	gaa	gaa	ctc	aat	tat		
Tyr	Ser	Leu	Tyr	Glu	His	Phe	Tyr	Leu	Ser	Ser	Glu	Glu	Leu	Asn	Tyr		
			580					585						590			
1824																	
agg	att	cac	ctt	aaa	gga	ctt	aca	ggg	aca	gcc	ggc	aaa	ata	agc	agc		
Arg	Ile	His	Leu	Lys	Gly	Leu	Thr	Gly	Thr	Ala	Gly	Lys	Ile	Ser	Ser		
		595					600					605					
1872																	
atc	agc	caa	cca	gga	aat	gat	ttt	agc	aca	aag	gat	gga	gac	aac	gac		
Ile	Ser	Gln	Pro	Gly	Asn	Asp	Phe	Ser	Thr	Lys	Asp	Gly	Asp	Asn	Asp		
	610					615					620						
1920																	
aaa	tgt	att	tgc	aaa	tgt	tca	caa	atg	cta	aca	gga	ggc	tgg	tgg	ttt		
Lys	Cys	Ile	Cys	Lys	Cys	Ser	Gln	Met	Leu	Thr	Gly	Gly	Trp	Trp	Phe		
	625				630					635					640		
1968																	
gat	gca	tgt	ggt	cct	tcc	aac	ttg	aac	gga	atg	tac	tat	cca	cag	agg		
Asp	Ala	Cys	Gly	Pro	Ser	Asn	Leu	Asn	Gly	Met	Tyr	Tyr	Pro	Gln	Arg		
				645					650					655			
2016																	
cag	aac	aca	aat	aag	ttc	aac	ggc	att	aaa	tgg	tac	tac	tgg	aaa	ggc		
Gln	Asn	Thr	Asn	Lys	Phe	Asn	Gly	Ile	Lys	Trp	Tyr	Tyr	Trp	Lys	Gly		
			660					665					670				
2064																	
tca	ggc	tat	tcg	ctc	aag	gcc	aca	acc	atg	atg	atc	cga	cca	gca	gat		
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675

680

685

2070

ttc tga
Phe

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<212> PRT
<213> Homo sapiens

<400> 8

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			20					25					30		
Thr	Leu	Thr	Phe	Pro	Asn	Ser	Thr	Glu	Glu	Ile	Lys	Ala	Tyr	Cys	Asp
		35					40					45			
Met	Glu	Ala	Gly	Gly	Gly	Gly	Trp	Thr	Ile	Ile	Gln	Arg	Arg	Glu	Asp
	50					55					60				
Gly	Ser	Val	Asp	Phe	Gln	Arg	Thr	Trp	Lys	Glu	Tyr	Lys	Val	Gly	Phe
65					70					75					80
Gly	Asn	Pro	Ser	Gly	Glu	Tyr	Trp	Leu	Gly	Asn	Glu	Phe	Val	Ser	Gln
				85					90					95	
Leu	Thr	Asn	Gln	Gln	Arg	Tyr	Val	Leu	Lys	Ile	His	Leu	Lys	Asp	Trp
			100					105					110		
Glu	Gly	Asn	Glu	Ala	Tyr	Ser	Leu	Tyr	Glu	His	Phe	Tyr	Leu	Ser	Ser
		115					120					125			
Glu	Glu	Leu	Asn	Tyr	Arg	Ile	His	Leu	Lys	Gly	Leu	Thr	Gly	Thr	Ala
	130					135					140				
Gly	Lys	Ile	Ser	Ser	Ile	Ser	Gln	Pro	Gly	Asn	Asp	Phe	Ser	Thr	Lys
145					150					155					160
Asp	Gly	Asp	Asn	Asp	Lys	Cys	Ile	Cys	Lys	Cys	Ser	Gln	Met	Leu	Thr
			165						170					175	
Gly	Gly	Trp	Trp	Phe	Asp	Ala	Cys	Gly	Pro	Ser	Asn	Leu	Asn	Gly	Met
		180						185				190			
Tyr	Tyr	Pro	Gln	Arg	Gln	Asn	Thr	Asn	Lys	Phe	Asn	Gly	Ile	Lys	Trp
		195					200					205			
Tyr	Tyr	Trp	Lys	Gly	Ser	Gly	Tyr	Ser	Leu	Lys	Ala	Thr	Thr	Met	Met
	210					215					220				
Ile	Arg	Pro	Ala	Asp	Phe	Gly	Gly	Pro	Gly	Glu	Pro	Lys	Ser	Cys	Asp
225					230					235					240
Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly
			245						250					255	
Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile
		260						265					270		
Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu
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Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His
	290					295					300				
Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg
305					310					315					320
Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys
			325						330					335	
Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu
		340						345					350		
Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr
		355					360					365			
Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu
	370					375					380				

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
 385 390 395 400
 Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
 405 410 415
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
 420 425 430
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
 435 440 445
 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
 450 455 460
 Gly Lys Gly Gly Gly Gly Ser Gly Ala Pro Arg Asp Cys Ala Glu Val
 465 470 475 480
 Phe Lys Ser Gly His Thr Thr Asn Gly Ile Tyr Thr Leu Thr Phe Pro
 485 490 495
 Asn Ser Thr Glu Glu Ile Lys Ala Tyr Cys Asp Met Glu Ala Gly Gly
 500 505 510
 Gly Gly Trp Thr Ile Ile Gln Arg Arg Glu Asp Gly Ser Val Asp Phe
 515 520 525
 Gln Arg Thr Trp Lys Glu Tyr Lys Val Gly Phe Gly Asn Pro Ser Gly
 530 535 540
 Glu Tyr Trp Leu Gly Asn Glu Phe Val Ser Gln Leu Thr Asn Gln Gln
 545 550 555 560
 Arg Tyr Val Leu Lys Ile His Leu Lys Asp Trp Glu Gly Asn Glu Ala
 565 570 575
 Tyr Ser Leu Tyr Glu His Phe Tyr Leu Ser Ser Glu Glu Leu Asn Tyr
 580 585 590
 Arg Ile His Leu Lys Gly Leu Thr Gly Thr Ala Gly Lys Ile Ser Ser
 595 600 605
 Ile Ser Gln Pro Gly Asn Asp Phe Ser Thr Lys Asp Gly Asp Asn Asp
 610 615 620
 Lys Cys Ile Cys Lys Cys Ser Gln Met Leu Thr Gly Gly Trp Trp Phe
 625 630 635 640
 Asp Ala Cys Gly Pro Ser Asn Leu Asn Gly Met Tyr Tyr Pro Gln Arg
 645 650 655
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 Ser Gly Tyr Ser Leu Lys Ala Thr Thr Met Met Ile Arg Pro Ala Asp
 675 680 685
 Phe

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48

gtc gtg tgg gcg ctg tgc cgg ctc gcc aca ccg ctg gcc aag aac ctg
 Val Val Trp Ala Leu Cys Arg Leu Ala Thr Pro Leu Ala Lys Asn Leu
 20 25 30

96

gag ccc gta tcc tgg agc tcc ctc aac ccc aag ttc ctg agt ggg aag
 Glu Pro Val Ser Trp Ser Ser Leu Asn Pro Lys Phe Leu Ser Gly Lys

144

09888677.100101

35	40	45	
ggc ttg gtg atc tat ccg aaa att gga gac aag ctg gac atc atc tgc			192
Gly Leu Val Ile Tyr Pro Lys Ile Gly Asp Lys Leu Asp Ile Ile Cys			
50	55	60	
ccc cga gca gaa gca ggg cgg ccc tat gag tac tac aag ctg tac ctg			240
Pro Arg Ala Glu Ala Gly Arg Pro Tyr Glu Tyr Tyr Lys Leu Tyr Leu			
65	70	75	80
gtg cgg cct gag cag gca gct gcc tgt agc aca gtt ctc gac ccc aac			288
Val Arg Pro Glu Gln Ala Ala Ala Cys Ser Thr Val Leu Asp Pro Asn			
	85	90	95
gtg ttg gtc acc tgc aat agg cca gag cag gaa ata cgc ttt acc atc			336
Val Leu Val Thr Cys Asn Arg Pro Glu Gln Glu Ile Arg Phe Thr Ile			
	100	105	110
aag ttc cag gag ttc agc ccc aac tac atg ggc ctg gag ttc aag aag			384
Lys Phe Gln Glu Phe Ser Pro Asn Tyr Met Gly Leu Glu Phe Lys Lys			
	115	120	125
cac cat gat tac tac att acc tca aca tcc aat gga agc ctg gag ggg			432
His His Asp Tyr Tyr Ile Thr Ser Thr Ser Asn Gly Ser Leu Glu Gly			
	130	135	140
ctg gaa aac cgg gag ggc ggt gtg tgc cgc aca cgc acc atg aag atc			480
Leu Glu Asn Arg Glu Gly Gly Val Cys Arg Thr Arg Thr Met Lys Ile			
145	150	155	160
atc atg aag gtt ggg caa gat ccc aat gct gtg acg cct gag cag ctg			528
Ile Met Lys Val Gly Gln Asp Pro Asn Ala Val Thr Pro Glu Gln Leu			
	165	170	175
act acc agc agg ccc agc aag gag gca gac aac act gtc aag atg gcc			576
Thr Thr Ser Arg Pro Ser Lys Glu Ala Asp Asn Thr Val Lys Met Ala			
	180	185	190
aca cag gcc cct ggt agt cgg ggc tcc ctg ggt gac tct gat ggc aag			624
Thr Gln Ala Pro Gly Ser Arg Gly Ser Leu Gly Asp Ser Asp Gly Lys			
	195	200	205
cat gag act gtg aac cag gaa gag aag agt ggc cca ggt gca agt ggg			672
His Glu Thr Val Asn Gln Glu Glu Lys Ser Gly Pro Gly Ala Ser Gly			
	210	215	220
ggc agc agc ggg gac cct gat ggc ttc ttc aac tcc aag ggc ccg ggt			720
Gly Ser Ser Gly Asp Pro Asp Gly Phe Phe Asn Ser Lys Gly Pro Gly			
225	230	235	240
aag aac ctg gag ccc gta tcc tgg agc tcc ctc aac ccc aag ttc ctg			768
Lys Asn Leu Glu Pro Val Ser Trp Ser Ser Leu Asn Pro Lys Phe Leu			
	245	250	255
agt ggg aag ggc ttg gtg atc tat ccg aaa att gga gac aag ctg gac			816
Ser Gly Lys Gly Leu Val Ile Tyr Pro Lys Ile Gly Asp Lys Leu Asp			
	260	265	270
atc atc tgc ccc cga gca gaa gca ggg cgg ccc tat gag tac tac aag			864
Ile Ile Cys Pro Arg Ala Glu Ala Gly Arg Pro Tyr Glu Tyr Tyr Lys			
	275	280	285

ctg tac ctg gtg cgg cct gag cag gca gct gcc tgt agc aca gtt ctc Leu Tyr Leu Val Arg Pro Glu Gln Ala Ala Cys Ser Thr Val Leu 290 295 300	912
gac ccc aac gtg ttg gtc acc tgc aat agg cca gag cag gaa ata cgc Asp Pro Asn Val Leu Val Thr Cys Asn Arg Pro Glu Gln Glu Ile Arg 305 310 315 320	960
ttt acc atc aag ttc cag gag ttc agc ccc aac tac atg ggc ctg gag Phe Thr Ile Lys Phe Gln Glu Phe Ser Pro Asn Tyr Met Gly Leu Glu 325 330 335	1008
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ctg gag ggg ctg gaa aac cgg gag ggc ggt gtg tgc cgc aca cgc acc Leu Glu Gly Leu Glu Asn Arg Glu Gly Gly Val Cys Arg Thr Arg Thr 355 360 365	1104
atg aag atc atc atg aag gtt ggg caa gat ccc aat gct gtg acg cct Met Lys Ile Ile Met Lys Val Gly Gln Asp Pro Asn Ala Val Thr Pro 370 375 380	1152
gag cag ctg act acc agc agg ccc agc aag gag gca gac aac act gtc Glu Gln Leu Thr Thr Ser Arg Pro Ser Lys Glu Ala Asp Asn Thr Val 385 390 395 400	1200
aag atg gcc acâ cag gcc cct ggt agt cgg ggc tcc ctg ggt gac tct Lys Met Ala Thr Gln Ala Pro Gly Ser Arg Gly Ser Leu Gly Asp Ser 405 410 415	1248
gat ggc aag cat gag act gtg aac cag gaa gag aag agt ggc cca ggt Asp Gly Lys His Glu Thr Val Asn Gln Glu Glu Lys Ser Gly Pro Gly 420 425 430	1296
gca agt ggg ggc agc agc ggg gac cct gat ggc ttc ttc aac tcc aaa Ala Ser Gly Gly Ser Ser Gly Asp Pro Asp Gly Phe Phe Asn Ser Lys 435 440 445	1344
ggc ccg ggc gag ccc aaa tct tgt gac aaa act cac aca tgc cca ccg Gly Pro Gly Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro 450 455 460	1392
tgc cca gca cct gaa ctc ctg ggg gga ccg tca gtc ttc ctc ttc ccc Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro 465 470 475 480	1440
cca aaa ccc aag gac acc ctc atg atc tcc cgg acc cct gag gtc aca Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr 485 490 495	1488
tgc gtg gtg gtg gac gtg agc cac gaa gac cct gag gtc aag ttc aac Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn 500 505 510	1536
tgg tac gtg gac ggc gtg gag gtg cat aat gcc aag aca aag ccg cgg Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg 515 520 525	1584

Lys	Phe	Gln	Glu	Phe	Ser	Pro	Asn	Tyr	Met	Gly	Leu	Glu	Phe	Lys	Lys	115	120	125
His	His	Asp	Tyr	Tyr	Ile	Thr	Ser	Thr	Ser	Asn	Gly	Ser	Leu	Glu	Gly	130	135	140
Leu	Glu	Asn	Arg	Glu	Gly	Gly	Val	Cys	Arg	Thr	Arg	Thr	Met	Lys	Ile	145	150	155
Ile	Met	Lys	Val	Gly	Gln	Asp	Pro	Asn	Ala	Val	Thr	Pro	Glu	Gln	Leu	165	170	175
Thr	Thr	Ser	Arg	Pro	Ser	Lys	Glu	Ala	Asp	Asn	Thr	Val	Lys	Met	Ala	180	185	190
Thr	Gln	Ala	Pro	Gly	Ser	Arg	Gly	Ser	Leu	Gly	Asp	Ser	Asp	Gly	Lys	195	200	205
His	Glu	Thr	Val	Asn	Gln	Glu	Glu	Lys	Ser	Gly	Pro	Gly	Ala	Ser	Gly	210	215	220
Gly	Ser	Ser	Gly	Asp	Pro	Asp	Gly	Phe	Phe	Asn	Ser	Lys	Gly	Pro	Gly	225	230	235
Lys	Asn	Leu	Glu	Pro	Val	Ser	Trp	Ser	Ser	Leu	Asn	Pro	Lys	Phe	Leu	245	250	255
Ser	Gly	Lys	Gly	Leu	Val	Ile	Tyr	Pro	Lys	Ile	Gly	Asp	Lys	Leu	Asp	260	265	270
Ile	Ile	Cys	Pro	Arg	Ala	Glu	Ala	Gly	Arg	Pro	Tyr	Glu	Tyr	Tyr	Lys	275	280	285
Leu	Tyr	Leu	Val	Arg	Pro	Glu	Gln	Ala	Ala	Ala	Cys	Ser	Thr	Val	Leu	290	295	300
Asp	Pro	Asn	Val	Leu	Val	Thr	Cys	Asn	Arg	Pro	Glu	Gln	Glu	Ile	Arg	305	310	315
Phe	Thr	Ile	Lys	Phe	Gln	Glu	Phe	Ser	Pro	Asn	Tyr	Met	Gly	Leu	Glu	325	330	335
Phe	Lys	Lys	His	His	Asp	Tyr	Tyr	Ile	Thr	Ser	Thr	Ser	Asn	Gly	Ser	340	345	350
Leu	Glu	Gly	Leu	Glu	Asn	Arg	Glu	Gly	Gly	Val	Cys	Arg	Thr	Arg	Thr	355	360	365
Met	Lys	Ile	Ile	Met	Lys	Val	Gly	Gln	Asp	Pro	Asn	Ala	Val	Thr	Pro	370	375	380
Glu	Gln	Leu	Thr	Thr	Ser	Arg	Pro	Ser	Lys	Glu	Ala	Asp	Asn	Thr	Val	385	390	395
Lys	Met	Ala	Thr	Gln	Ala	Pro	Gly	Ser	Arg	Gly	Ser	Leu	Gly	Asp	Ser	405	410	415
Asp	Gly	Lys	His	Glu	Thr	Val	Asn	Gln	Glu	Glu	Lys	Ser	Gly	Pro	Gly	420	425	430
Ala	Ser	Gly	Gly	Ser	Ser	Gly	Asp	Pro	Asp	Gly	Phe	Phe	Asn	Ser	Lys	435	440	445
Gly	Pro	Gly	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	450	455	460
Cys	Pro	Ala	Pro	Glu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro		465	470	475
Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	485	490	495
Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	500	505	510
Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	515	520	525
Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	530	535	540
Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	545	550	555
Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	565	570	575
Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	580	585	590
Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe			

Leu	Glu	Gly	Leu	Asp	Asn	Gln	Glu	Gly	Gly	Val	Cys	Gln	Thr	Arg	Ala			
145					150					155					160			
atg	aag	atc	ctc	atg	aaa	gtt	gga	caa	gat	gca	agt	tct	gct	gga	tca			528
Met	Lys	Ile	Leu	Met	Lys	Val	Gly	Gln	Asp	Ala	Ser	Ser	Ala	Gly	Ser			
				165					170					175				
gcc	agg	aat	cac	ggt	cca	aca	aga	cgt	cca	gag	cta	gaa	gct	ggt	aca			576
Ala	Arg	Asn	His	Gly	Pro	Thr	Arg	Arg	Pro	Glu	Leu	Glu	Ala	Gly	Thr			
			180					185					190					
aat	ggg	aga	agt	tca	aca	aca	agt	ccc	ttt	gtg	aag	cca	aat	cca	ggt			624
Asn	Gly	Arg	Ser	Ser	Thr	Thr	Ser	Pro	Phe	Val	Lys	Pro	Asn	Pro	Gly			
			195				200					205						
tct	agc	acc	gat	ggc	aac	agc	gcg	ggg	cat	tcc	ggg	aac	aat	ctc	ctg			672
Ser	Ser	Thr	Asp	Gly	Asn	Ser	Ala	Gly	His	Ser	Gly	Asn	Asn	Leu	Leu			
			210			215					220							
ggg	ggc	ccg	gga	ata	gtt	tta	gag	cct	atc	tac	tgg	aat	tcc	tcg	aac			720
Gly	Gly	Pro	Gly	Ile	Val	Leu	Glu	Pro	Ile	Tyr	Trp	Asn	Ser	Ser	Asn			
225				230					235					240				
tcc	aaa	ttt	cta	ccc	gga	caa	ggc	ctg	gta	cta	tac	cca	cag	ata	gga			768
Ser	Lys	Phe	Leu	Pro	Gly	Gln	Gly	Leu	Val	Leu	Tyr	Pro	Gln	Ile	Gly			
				245				250						255				
gac	aaa	ttg	gat	att	att	tgc	ccc	aaa	gtg	gac	tct	aaa	act	gtt	ggc			816
Asp	Lys	Leu	Asp	Ile	Ile	Cys	Pro	Lys	Val	Asp	Ser	Lys	Thr	Val	Gly			
			260					265					270					
cag	tat	gaa	tat	tat	aaa	gtt	tat	atg	gtt	gat	aaa	gac	caa	gca	gac			864
Gln	Tyr	Glu	Tyr	Tyr	Lys	Val	Tyr	Met	Val	Asp	Lys	Asp	Gln	Ala	Asp			
			275				280					285						
aga	tgc	aca	att	aag	aag	gag	aat	acc	ccg	ctg	ctc	aac	tgt	gcc	aga			912
Arg	Cys	Thr	Ile	Lys	Lys	Glu	Asn	Thr	Pro	Leu	Leu	Asn	Cys	Ala	Arg			
			290			295				300								
cca	gac	caa	gat	gtg	aaa	ttc	acc	atc	aag	ttt	caa	gaa	ttc	agc	cct			960
Pro	Asp	Gln	Asp	Val	Lys	Phe	Thr	Ile	Lys	Phe	Gln	Glu	Phe	Ser	Pro			
305				310					315					320				
aac	ctc	tgg	ggt	cta	gaa	ttt	cag	aag	aac	aaa	gat	tac	tac	att	ata			1008
Asn	Leu	Trp	Gly	Leu	Glu	Phe	Gln	Lys	Asn	Lys	Asp	Tyr	Tyr	Ile	Ile			
				325					330					335				
tct	aca	tca	aat	ggg	tct	ttg	gag	ggc	ctg	gat	aac	cag	gag	gga	ggg			1056
Ser	Thr	Ser	Asn	Gly	Ser	Leu	Glu	Gly	Leu	Asp	Asn	Gln	Glu	Gly	Gly			
			340					345					350					
gtg	tgc	cag	aca	aga	gcc	atg	aag	atc	ctc	atg	aaa	gtt	gga	caa	gat			1104
Val	Cys	Gln	Thr	Arg	Ala	Met	Lys	Ile	Leu	Met	Lys	Val	Gly	Gln	Asp			
			355			360						365						
gca	agt	tct	gct	gga	tca	gcc	agg	aat	cac	ggt	cca	aca	aga	cgc	cca			1152
Ala	Ser	Ser	Ala	Gly	Ser	Ala	Arg	Asn	His	Gly	Pro	Thr	Arg	Arg	Pro			
			370			375					380							
gag	cta	gaa	gct	ggt	aca	aat	ggg	aga	agt	tca	aca	aca	agt	ccc	ttt			1200
Glu	Leu	Glu	Ala	Gly	Thr	Asn	Gly	Arg	Ser	Ser	Thr	Thr	Ser	Pro	Phe			

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385	390	395	400	
gtg aag cca aat cca ggt tct agc acc gat ggc aac agc gcg ggg cat				1248
Val Lys Pro Asn Pro Gly Ser Ser Thr Asp Gly Asn Ser Ala Gly His	405	410	415	
tcc ggg aac aat ctc ctg ggg ggc ccg ggc gag ccc aaa tct tgt gac				1296
Ser Gly Asn Asn Leu Leu Gly Gly Pro Gly Glu Pro Lys Ser Cys Asp	420	425	430	
aaa act cac aca tgc cca ccg tgc cca gca cct gaa ctc ctg ggg gga				1344
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly	435	440	445	
ccg tca gtc ttc ctc ttc ccc cca aaa ccc aag gac acc ctc atg atc				1392
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile	450	455	460	
tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac gtg agc cac gaa				1440
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu	465	470	475	480
gac cct gag gtc aag ttc aac tgg tac gtg gac ggc gtg gag gtg cat				1488
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His	485	490	495	
aat gcc aag aca aag ccg cgg gag gag cag tac aac agc acg tac cgt				1536
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg	500	505	510	
gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg aat ggc aag				1584
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys	515	520	525	
gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca gcc ccc atc gag				1632
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu	530	535	540	
aaa acc atc tcc aaa gcc aaa ggg cag ccc cga gaa cca cag gtg tac				1680
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr	545	550	555	560
acc ctg ccc cca tcc cgg gat gag ctg acc aag aac cag gtc agc ctg				1728
Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu	565	570	575	
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Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp	580	585	590	
gag agc aat ggg cag ccg gag aac aac tac aag acc acg cct ccc gtg				1824
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val	595	600	605	
ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc acc gtg gac				1872
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp	610	615	620	
aag agc agg tgg cag cag ggg aac gtc ttc tca tgc tcc gtg atg cat				1920
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His	625	630	635	640

gag gct ctg cac aac cac tac acg cag aag agc ctc tcc ctg tct ccg
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1968

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 Gly Lys

1977

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 35 40 45
 Gln Gly Leu Val Leu Tyr Pro Gln Ile Gly Asp Lys Leu Asp Ile Ile
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 Cys Pro Lys Val Asp Ser Lys Thr Val Gly Gln Tyr Glu Tyr Tyr Lys
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 Val Tyr Met Val Asp Lys Asp Gln Ala Asp Arg Cys Thr Ile Lys Lys
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 Asn Gly Arg Ser Ser Thr Thr Ser Pro Phe Val Lys Pro Asn Pro Gly
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 Ser Lys Phe Leu Pro Gly Gln Gly Leu Val Leu Tyr Pro Gln Ile Gly
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 Asp Lys Leu Asp Ile Ile Cys Pro Lys Val Asp Ser Lys Thr Val Gly
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 Gln Tyr Glu Tyr Tyr Lys Val Tyr Met Val Asp Lys Asp Gln Ala Asp
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